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# Dissociation of lung function, dyspnea ratings and pulmonary extension in bronchiectasis

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Received 22 January 2007; accepted 29 June 2007

Available online 14 August 2007

## KEYWORDS

Bronchiectasis;  
Factor analysis;  
Dissociation;  
Dyspnea;  
*Pseudomonas  
aeruginosa*

## Summary

Bronchiectasis is a heterogeneous disease in terms of its clinical and functional presentation. Some isolated parameters have been used to assess the severity of bronchiectasis or its response to treatment. A study was undertaken to evaluate whether lung function, dyspnea and extension of the disease are separate entities in the impact of bronchiectasis upon patients using factor analysis.

Patients with bronchiectasis diagnosed by high-resolution computed tomography (HRCT) and airflow obstruction defined by  $FEV_1/FVC < 70\%$  were included. Data were collected relating to clinical history, three different clinical ratings of dyspnea (Medical Research Council (MRC), Borg scale and Basal Dyspnea Index), the extent of bronchiectasis and functional variables.

A total of 81 patients (mean age (SD): 69.5 (8.7)) years were included. The degree of dyspnea (MRC) was 1.9 (0.8). Mean  $FEV_1$  was 1301 ml (56.9% pred.). Four factors were found that accounted for 84.1% of the total data variance. Factor 1 (45.6% of the data variance) included the three measurements of dyspnea. Factor 2 (16% variance) comprised airflow obstruction parameters ( $FEV_1$ ,  $FEV_1/FVC$  and PEF). Factor 3 (13.8% variance) included RV/TLC and RV (lung hyperinflation). Factor 4 (8.6% variance) included bronchiectasis extent. Dyspnea was more closely correlated with lung hyperinflation ( $r: 0.33–0.54$ ) than with airflow obstruction parameters ( $r: 0.17–0.26$ ).

**Conclusions:** Airflow obstruction, dyspnea, lung hyperinflation and the lung extent of the bronchiectasis are four independent entities in the impact of bronchiectasis upon patients.

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## Introduction

Bronchiectasis is a chronic lung condition characterized by irreversible bronchial dilatation due to a vicious circle comprising clearance system damage, inflammation and infection of the bronchi.<sup>1</sup> In evolutive terms, bronchiectasis behaves as a chronic and progressive disease with multiple exacerbations and chronic colonization of the bronchial mucosa by different pathogenic microorganisms. The ultimate result is altered lung function (generally comprising irreversible airflow obstruction) and progressive dyspnea that greatly deteriorates patient's quality of life.<sup>2-4</sup>

Several isolated parameters such as functional or microbiological variables, clinical data or the extent of the disease have been used to assess the severity of disease or to evaluate the effect of several treatments in patients with steady-state bronchiectasis.<sup>5-7</sup> However, the impact of bronchiectasis varies considerably between patients—as indicated by the great variability in the clinical picture or quality of life scores in relation to the same lung function or extent of bronchiectasis.<sup>3,8,9</sup> This seems to indicate that a single clinical or functional parameter does not suffice to assess the global effects of bronchiectasis upon patients.

Factor analysis has been shown to be a useful statistical tool as a hypothesis-generating technique for analyzing the relationship between multiple measures in evaluating outcome in clinical studies. It has already been successfully used by some authors for studying other airway disorders such as chronic obstructive pulmonary disease (COPD) or asthma. For example, in patients with asthma, factor analysis has demonstrated that lung function, airway hyper-responsiveness and eosinophilic inflammation in sputum are non-overlapping dimensions.<sup>10</sup> In COPD, factor analysis has been applied to study the dissociation between lung function, the clinical rating of dyspnea, exercise capacity and lung hyperinflation.<sup>11-13</sup> There is growing controversy about the relationships between lung function, clinical features—especially dyspnea—and the radiological extension of disease in patients with bronchiectasis. These intervariable relationships have usually been analyzed using simple correlations; we have not found any studies using factor analysis to assess the multivariate relationship among these baseline conditions in patients with bronchiectasis.

The present study was designed to analyze whether lung function, the clinical rating of dyspnea and lung extension of bronchiectasis as assessed by high-resolution computed tomography (HRCT) are separate entities offering independent information for assessment of the impact of bronchiectasis upon patients. For this purpose we applied factor analysis in well-characterized patients with non-cystic fibrosis (CF) steady-state bronchiectasis and airflow obstruction exhibiting a broad range of disease severity.

## Methods

### Study population

One hundred and thirty-one patients diagnosed in our center with clinically stable bronchiectasis affecting more than one lung lobe, or with cystic bronchiectasis, were asked to participate in the study. All patients were sent to our

out-patient clinic due to symptoms attributable to bronchiectasis. Patients with traction bronchiectasis associated to advanced interstitial processes ( $n = 15$ ) were excluded, as were patients with bronchiectasis subjected to surgical management ( $n = 2$ ), individuals who because of mental or physical impairment were presumed to be unable to complete the study protocol ( $n = 11$ ) and patients who refused to participate ( $n = 2$ ). Finally, patients without airflow obstruction defined as a  $FEV_1/FVC < 70\%$  were also excluded ( $n = 21$ ). Exacerbation was defined as persistent ( $> 24$  h) deterioration of at least three respiratory symptoms (including cough, dyspnea, hemoptysis, increased sputum purulence or volume, and chest pain) with or without fever, radiographic deterioration, systemic disturbances, or deterioration in chest signs.<sup>6</sup> The study protocol was approved by our Ethics Committee and is consistent with the principles of the Declaration of Helsinki.

### Dyspnea evaluation

All patients finally included in the study were seen in our center during 2003 for documentation of the complete clinical history (CH visit), which included general and anthropometric data (age, sex and body mass index (BMI) in  $kg/m^2$ ), and personal disease antecedents of interest and smoking habit (packs/year). Dyspnea was evaluated prior to functional testing using three validated scales: a modified Medical Research Council (MRC) scale,<sup>14</sup> the Borg scale<sup>15</sup> and the Basal Dyspnea Index (BDI).<sup>16</sup> The modified MRC scale includes five grades of various physical activities that provoke dyspnea. The BDI consists of 5 grades for the categories: functional impairment, magnitude of task and magnitude of effort. The Borg scale is a visual analog scale (VAS) of dyspnea which was represented as a value ranging from 0 to 10 (10 = maximum dyspnea).

### Diagnosis and extent of bronchiectasis

Bronchiectasis was diagnosed by HRCT of the chest, with 1 mm slices at 10 mm intervals in deep inspiration, according to the criteria of Naidich et al.<sup>17</sup> The extent of bronchiectasis was established by a modified scale described by Bhalla et al.<sup>18</sup>: each lung lobe (considering lingula and middle lobe as independent) was scored as 0 (no bronchiectasis), 1 (cylindrical bronchiectasis in a single lung segment), 2 (cylindrical bronchiectasis in more than one lung segment) or 3 (cystic bronchiectasis). The maximum score was taken to be 18 points. All HRCT scans were independently evaluated by two radiologists with extensive experience in the study of HRCT images of bronchiectatic patients. Kappa value was calculated for assessment of interobserver agreement for the diagnosis of bronchiectasis.

### Lung function measurement

Lung function testing was performed over the 2 days following the CH visit, and included forced spirometry with the measurement of forced expiratory volume in one second ( $FEV_1$ ), forced vital capacity (FVC) and peak expiratory flow (PEF) according to the Spanish Society of Respiratory Disease (SEPAR) guidelines.<sup>19</sup> Flow obstruction was defined as the

presence of  $FEV_1/FVC < 70\%$ . Total lung capacity (TLC) and residual volume (RV) were measured by the helium dilution technique. The RV/TLC ratio was accepted as a measure of pulmonary hyperinflation. Reference values for all lung function measurements were obtained from Roca et al. for a mediterranean population.<sup>20</sup> All tests were performed by qualified staff and at the same time in the morning. The patients were required to be in a clinically stable phase (at least 4 weeks without exacerbation) for conducting any clinical or functional test.

### Exploratory factor analysis

The SPSS version 11.0 statistical package (SPSS, Chicago, IL) for Microsoft Windows was used throughout. The data were tabulated as the mean, standard deviation (SD) and range for quantitative variables, and as the absolute value and percentage in the case of qualitative variables.

A set of nine variables related to lung function ( $FEV_1$ , PEF,  $FEV_1/FVC$ , RV and RV/TLC all expressed as the percentage of predicted value), dyspnea measurements (MRC, Borg scale and BDI) and the radiological extent of bronchiectasis assessed by HRCT score were selected to be included in the factor analysis. The initial step was the creation of a Pearson's correlation matrix of all the nine variables. The possibility to perform factor analysis was tested by Bartlett's test of sphericity, and the Kaiser–Meyer–Olkin (KMO) test was applied. Factor analysis was then used to determine the components underlying the pattern of interrelationships among variables without reference to a specific criterion. The purpose of this procedure was to attribute the variables to independent hypothetical factors. The number of factors was based on the number of eigenvalues  $> 1$  (an index of the proportion of variance explained by successive factors, whose magnitude was  $> 1$  of the Scree plot). The coefficients that link variables to factors are referred to as "factor loading", and constitute the correlation coefficients between variables and factors. The varimax rotation procedure was used to maximize the loadings of each variable on one factor, whilst simultaneously minimizing the loadings on the other factors in order to increase the interpretability of the factors. Thus, in essence, variables are separated into different factors with independent information about the disease (called dimensions of the disease). By examining which variables loaded highly on each factor, the factors were interpreted and named. We conducted three additional factor analyses to determine the stability of the factor structures, and thus the robustness of our findings. First, we repeated the analysis including only patients with chronic colonization of sputum by *Pseudomonas aeruginosa* (PA) or *Haemophilus influenzae* (HI). This was followed by inclusion of only never-smoking patients and finally using the absolute values of the functional parameters instead of the percentage of predicted values.

## Results

### Patient characteristics

Eighty-one patients were finally included in the study, with a mean (SD) age of 69.5 (8.75) years; 52% were males. Five

patients (6.2%) were current smokers (33 packs/year), and 34 patients (41.9%) were former smokers (20.2 packs/year). The identified etiologies were: idiopathic 37 (45.6%), post-infection 24 (29.6%); post-tuberculosis 13 (16%); allergic bronchopulmonary aspergillosis 3 (3.7%); and rheumatoid arthritis, immotile cilia syndrome, post-measles and polymyositis with a single case each. Mean values, standard deviation and ranges for clinical ratings of dyspnea, lung function parameters and HCRT extension score are listed in Table 1. Agreement between the two radiologist was excellent for the detection of bronchiectasis by HRCT scan (kappa: 0.81).

### Pearson's correlation matrix

All clinical ratings of dyspnea showed weak or no significant correlation with spirometric function parameters (range of correlation coefficients 0.18–0.29). However, all measurements of dyspnea—especially the MRC and BDI scores—correlated with lung hyperinflation measures (range of correlation coefficients 0.33–0.54). On the other hand, the lung extension of bronchiectasis as assessed by the HRCT score showed weak or no significant correlation with clinical rating of dyspnea or lung function parameters (Table 2).

### Factor analysis

The factor analysis of available data yielded four meaningful independent factors, with eigenvalues of 3.63, 1.28, 1.12 and 1.07, respectively, which accounted for 84.1% of the variance. The possibility of performing factor analysis was confirmed by a statistically significant Bartlett's test of sphericity ( $p < 0.0001$ ), and a KMO test value of 0.662.

**Table 1** Patient characteristics ( $n = 81$ ).

Parameter	Mean (SD)	Range
Age (yr)	69.5 (8.7)	45–84
Gender M/F	42/39	–
BMI ( $kg/m^2$ )	28.7 (4.6)	19–41
Dyspnea (MRC)	1.91 (0.88)	0–4
Dyspnea (Borg)	3.44 (1.68)	0–9
Dyspnea (BDI)	6.54 (2.75)	0–12
$FEV_1$ (% predicted)	56.9 (19.4)	17–98
$FEV_1$ (ml)	1301.8 (519)	495–2810
$FEV_1/FVC$	55.1 (10.6)	30.8–69.8
RV (% predicted)	111.8 (32.34)	59–276.3
RV/TLC	125.7 (35.1)	80.9–254.1
HRCT score	4.53 (2.3)	2–14

Quantitative variables were tabulated as the mean, standard deviation (SD) and range, and qualitative variables as the absolute value and percentage.

HRCT: high-resolution computed tomography of the chest; MRC: Medical Research Council dyspnea scale; Postbd: post-bronchodilator values;  $FEV_1$ : forced expiratory volume in 1 s; RV/TLC: ratio between residual volume and total lung capacity.

**Table 2** Pearson's correlation matrix of clinical rating of dyspnea, lung function parameters and disease extension score.

Parameter	Dyspnea (MRC)	Dyspnea (BDI)	Dyspnea (Borg)	HRCT score
FEV <sub>1</sub> (% pred.)	−0.26*	0.27*	−0.17	−0.19
FEV <sub>1</sub> /FVC	−0.23*	0.22*	−0.19	−0.20
PEF (l/min)	−0.17	0.19	−0.20	−0.14
RV/TLC	0.54 <sup>†</sup>	−0.51 <sup>†</sup>	0.45 <sup>†</sup>	0.17
RV	0.46 <sup>†</sup>	−0.41*	0.33 <sup>†</sup>	0.12
HRCT score	0.27*	−0.09	0.15	—

FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s; PEF: peak expiratory flow; MRC: Medical Research Council scale; BDI: Basal Dyspnea Index; RV/TLC: ratio between residual volume and total lung capacity; HRCT: high-resolution computed tomography of the chest.

\* $p < 0.05$ .

<sup>†</sup> $p < 0.01$ .

**Table 3** Varimax rotated factor-loading matrix for all the 81 patients.

	Factor 1 (dyspnea)	Factor 2 (airflow obstruction)	Factor 3 (lung hyperinflation)	Factor 4 (extension)
Dyspnea (BDI)	<b>−0.910</b>	0.198	−0.320	0.010
Dyspnea (MRC)	<b>0.878</b>	−0.133	0.405	0.038
Dyspnea (Borg)	<b>0.660</b>	−0.114	0.312	0.125
FEV <sub>1</sub> /FVC	−0.115	<b>0.918</b>	−0.230	0.023
FEV (% pred.)	−0.217	<b>0.816</b>	−0.242	−0.116
PEF	−0.123	<b>0.808</b>	−0.198	−0.102
RV	0.412	−0.294	<b>0.881</b>	−0.013
RV/TLC	0.483	−0.116	<b>0.717</b>	0.021
HRCT score	−0.064	−0.173	−0.054	<b>0.957</b>
<i>Eigenvalue</i>	3.63	1.28	1.12	1.07
% Variance	45.6	16	13.8	8.6

FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s; PEF: peak expiratory flow; MRC: Medical Research Council scale; BDI: Basal Dyspnea Index; RV/TLC: ratio between residual volume and total lung capacity; HRCT: high-resolution computed tomography of the chest. The loading factors of the variables assigned to each factor are shown in boldface.

## Dyspnea factor

The first factor appeared to be “*dyspnea*”. It comprised all three clinical ratings of dyspnea (MRC, BDI and Borg scale), which account for 45.6% of the variance. RV and RV/TLC (particularly the latter ratio) showed significant additional loading on the “*dyspnea*” factor.

## Functional factors

Airflow obstruction parameters including FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and PEF as percentages of predicted values loaded on a second factor which accounted for 16% of the variance. Pulmonary hyperinflation variables (RV and RV/TLC) loaded predominantly on a third factor and were able to explain 13.8% of the variance. Dyspnea measurements, especially the MRC scale, loaded significantly on this factor.

## Extension factor

The last factor comprised a single variable—HRCT bronchiectasis extension score—and was thus referred to as the

“*lung extent*” factor (explaining 8.6% of the total variance) (Table 3).

## Subgroup factor analyses

When the analysis was repeated with absolute values of lung function parameters instead of theoretical predicted values (KMO test value of 0.591), the results did not significantly change. Similarly, results were not altered by dividing the total sample of patients on the basis of the presence or not of chronic colonization of the sputum by any potential pathogenic microorganisms, especially *P. aeruginosa* or *H. influenzae* ( $n = 49$ ), and repeating the factor analysis in both subgroups (KMO test values of 0.573 and 0.599, respectively)—though these patients, and especially the PA subgroup, presented more disease severity in terms of disease extension of the disease (HRCT score: 5.07 vs. 3.68;  $p < 0.01$ ), dyspnea score (MRC: 2.31 vs. 1.55;  $p < 0.01$ ) and airflow obstruction (FEV<sub>1</sub> (% predicted): 50.1 vs. 61.5,  $p < 0.01$ ). In the same way, factor patterns were not altered when the subgroup of never-smoking patients ( $n = 42$ ) was analyzed separately (KMO test value of 0.563). Factor



analysis performed in all studied subgroups showed a statistically significant Bartlett's test of sphericity ( $p < 0.0001$ ). Since pulmonary hyperinflation variables significantly loaded on the "dyspnea" factor, an additional factor analysis was performed with the same data in which three factors were selected *a priori* (KMO test value of 0.588). The three measurements of dyspnea and pulmonary hyperinflation variables loaded predominantly only on one factor, resulting in a significant decrease in the total explained variance to 70.8%; the four-factor analysis was thus selected as a main outcome of the study.

## Discussion

Using factor analysis, we found that dyspnea measurements, airflow obstruction, lung hyperinflation and pulmonary extension of bronchiectasis were four statistically independent and clinically interpretable dimensions or entities characterizing patients with non-CF steady-state bronchiectasis. The perception of dyspnea in patients with bronchiectasis is more closely related to lung hyperinflation assessed by RV/TLC than to lung obstruction severity as assessed by FEV<sub>1</sub>/FVC and FEV<sub>1</sub>. To our knowledge, this is the first study combining functional parameters, clinical aspects and the pulmonary extent of bronchiectasis in factor analysis to explore multivariable relationships among outcomes in patients with non-CF bronchiectasis.

Several single parameters including airflow obstruction, dyspnea scores, chronic PA colonization of sputum or the extent of the disease have been used to assess the severity of the disease or to evaluate the effect of treatment in patients with bronchiectasis.<sup>5-7</sup> However, evaluation of the severity or course of the disease based on a single parameter is usually insufficient. Thus, while the diagnosis of bronchiectasis is merely morphological, its effects upon the patient seem to comprise a series of components or dimensions with different relative influences. Our results, using factor analysis, showed that dyspnea scores, airway obstruction parameters, pulmonary hyperinflation and HRCT extension of bronchiectasis are non-overlapping dimensions suggesting that the evaluation of patients with non-CF bronchiectasis should include measurements of all these parameters. Some clinical applications of this finding would be to analyze which domains improve as a result of therapeutic intervention and to analyze the patterns of improvement, or to create a weighted severity score specific to the disease, using the information from each of the domains studied in the factorial analysis.

The first factor included the three different clinical ratings of dyspnea (MRC, Borg and BDI). Interestingly, dyspnea, in the same way as has been observed in other obstructive airway diseases such as COPD,<sup>11,21</sup> was much more closely related to pulmonary hyperinflation than to airflow obstruction assessed by FEV<sub>1</sub>/FVC and FEV<sub>1</sub> according to the significant additional loading of RV/TLC and RV values on this factor. Although dyspnea in bronchiectasis is probably a multidimensional phenomenon with some underlying mechanism of production such as airflow obstruction, mucus retention or psychological factors, the relationship between dyspnea and lung hyperinflation found in our study seems to afford information on another important physio-

pathological mechanism underlying dyspnea in these patients: inefficient respiratory muscle function under conditions of air trapping. Of note is the observation that the Borg scale was found to have the worst loading on the "dyspnea" factor and the worst correlation with functional variables—probably reflecting the fact that the Borg scale evaluates a different aspect of dyspnea than that evaluated by other dyspnea ratings in patients with bronchiectasis.

The second factor included FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and PEF as expression of the different severity of airflow obstruction. Our data were consistent with other studies on bronchiectasis in relation to the notion that airway obstruction indexes are independent of clinical variables,<sup>3,8</sup> since these parameters loaded on different factors in our study. On the other hand, we have not found any relationship between lung obstruction parameters and HRCT extension of bronchiectasis, in coincidence with other studies which have usually shown correlation coefficients below 0.4.<sup>5,22</sup> We have eliminated age, height, and gender as explicit variables in our factor analysis, by referring the lung function parameters to their respective reference values.

Our third identified factor included RV and RV/TLC values, and was called "pulmonary hyperinflation". Of note is the observation that this factor is clearly separated from the "airflow obstruction" factor, as indicated by its loadings indicating that in patients with non-CF bronchiectasis in the same way as COPD,<sup>11,21</sup> hyperinflation is an independent characteristic of the disease state that is not always directly linked to airway obstruction. This lack of relationship observed in our study could be explained by the different mechanisms of production of both phenomena. Roberts et al.<sup>22</sup> showed airflow obstruction in bronchiectasis assessed by FEV<sub>1</sub> and FEV<sub>1</sub>/FVC to be related fundamentally to bronchial wall thickening and increased bronchial secretions in large airways, while the presence of small airway alterations such as bronchiolectasis, bronchiolar mucus plugging and especially bronchiolitis—which cause functional disturbances usually not detected by simple forced spirometry—were more related to lung hyperinflation. In this sense, Kang et al.<sup>23</sup> found in lung resected specimens that extended histological evidence of bronchiolitis as an associated finding of bronchiectasis was present in 85% of the lung lobes studied.

The last factor was the "extent" factor, and loaded only one variable: the HRCT score. It would seem logical to assume that the pulmonary extent of bronchiectasis is a key determinant factor in defining the characteristics of bronchiectasis disease. However, some studies appear to suggest that the radiological extent of bronchiectasis is only weakly correlated to the symptoms or to lung function.<sup>5,22</sup> This was also suggested by our own results, where the extent of bronchiectasis was seen to be a largely independent factor accounting for only a small part of the observed variance, and with no relationship to other clinical or functional variables even in the bivariate correlation analysis.

To increase the robustness of our findings, we included in the analysis a broad range of disease severity in relation to dyspnea, airflow obstruction (FEV<sub>1</sub> (% predicted) from 17% to 98%) and radiological extent of bronchiectasis. Moreover, we repeated the factor analysis under three different settings: using the absolute values of lung function instead of the

percentage of predicted values; including only the subgroup of patients with chronic colonization of sputum by PA or HI as an expression of increased disease severity; and finally including only never-smoking patients in order to reasonably exclude COPD. We found no significant changes in the pattern of factors in any of the subanalyses or in the relationships between variables belonging to different factors. Therefore, our analysis appeared to be fairly stable even if additional parameters were taken into account or different subgroups were studied, although it should be mentioned that as a consequence of the reduced number of patients in each of the sub-groups studied, these results may be less reliable. There are some limitations in this study which should be mentioned. On one hand, evolutive variables, such as clinical evolution, mortality or the number of exacerbations, were not included in our analysis due to the transversal nature of the study. On the other hand, important transversal variables related to bronchiectasis, such as sputum volume, etiology, inflammatory status or quality of life, were not included in the analysis because the limited number of patients did not allow the inclusion of more variables in the factorial analysis. The variables selected (pulmonary function, dyspnea, and pulmonary extension of disease) were influenced, first, by the controversy in the literature over the association between these variables in patients with bronchiectasis and, second, because these are the three most commonly used variables for evaluating severity in these types of patients.

In conclusion, our data clearly suggest that dyspnea, airflow obstruction, pulmonary hyperinflation and pulmonary extension of bronchiectasis are four independent entities offering separate and additive information on the pathological condition in patients with non-CF bronchiectasis. Dyspnea correlates better with lung hyperinflation than with lung obstruction—suggesting that airflow trapping could be an important mechanism of dyspnea in patients with bronchiectasis. We think that our study provides important information for the designing of future studies to assess the effect upon clinical or functional outcomes of different therapeutic interventions in patients with non-CF bronchiectasis.

## Conflict of interest

Financial support for the present study was provided by a public institution. The authors of the manuscript therefore have no conflict of interest to declare.

## Financial support

This study has been supported in part by a grant: Redrespira-ISCiii-RTIC-03/11 (Spanish Ministry of Health).

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